Responsiveness of the ductus arteriosus to prostaglandin E₁ assessed by combined cross sectional and pulsed Doppler echocardiography

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SUMMARY Cross sectional echocardiography combined with Doppler echocardiography was used to record either ductal morphology or the flow profile within the ductus arteriosus before and after infusion of prostaglandin E₁ in 25 newborn infants with cyanotic and acyanotic congenital heart disease with ductus dependent blood flow. The ultrasound results were compared with changes in arterial oxygen tension and the overall clinical response to prostaglandin E₁ seen during the same period in 24 of the 25 patients in whom the degree of ductal narrowing could be determined with the ultrasound method. At the time of the study, the ductus was widely patent or slightly narrowed in 12 patients and was closed in two patients. These patients did not respond to prostaglandin E₁.

There was prominent localised narrowing of the ductus in seven patients and generalised narrowing in three. After the infusion of prostaglandin E₁ there was no ductal narrowing in these patients, except for one patient who had slight residual localised narrowing. There was also a considerable change in the ductal flow profiles in each patient. In these 10 patients infusion of prostaglandin E₁ resulted in an increase in arterial oxygen tension, clinical improvement, or both.

The present study indicates that prostaglandin E₁ is effective in patients with prominent narrowing of the ductus but is not in patients in whom the ductus is widely patent or closed. Cross sectional echocardiography combined with Doppler echocardiography was useful for predicting the responsiveness of the ductus arteriosus to the infusion.

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Accepted for publication 21 February 1989
two patients with hypoplastic left heart syndrome, which was diagnosed by cross sectional echocardiography alone. The patients were divided into four groups (table). Group 1 consisted of 10 patients with ducus dependent pulmonary blood flow (simple or complex pulmonary atresia and critical pulmonary stenosis). Group 2 consisted of seven patients with ducus dependent systemic venous mixing (complete transposition of the great arteries with intact ventricular septum and atrial septal defect or persistent foramen ovale). Group 3 consisted of seven patients with ducus dependent systemic blood flow (coartation of aorta and hypoplastic left heart syndrome). The only patient in group 4 had total anomalous pulmonary venous connection with venous obstruction in which the descending vein terminated in the hepatic vein, and with no other associated anomaly. In this patient, treatment with prostaglandin E₁ was started on the basis of Doppler determined ducal flow profiles and clinical deterioration. The efficacy of prostaglandin E₁ in the patients in groups 1 and 2 was assessed by changes in arterial oxygen tension. Arterial oxygen tension was usually measured immediately before and several times after the start of the infusion. When more than one value was obtained after the onset of the infusion, the value obtained closest to one hour after the start of the infusion was used for the analysis. The overall clinical effects of the infusion in the patients in groups 3 and 4 were evaluated by changes in blood pressure in the arms and legs, urine flow, and serial chest x ray films. In two infants with simple coartation of the aorta, the systolic pressures in the femoral and radial arteries were monitored simultaneously throughout the period of infusion.

**CROSS SECTIONAL AND DOPPLER ECHOCARDIOGRAPHIC STUDIES**

All patients were studied with a pulsed Doppler echocardiographic system (Hewlett Packard, Model 77020 AC) with a 5 MHz shallow focus transducer immediately before and several times after the start of infusion of prostaglandin E₁. The data obtained closest to one hour after the start of the infusion were used to compare arterial oxygen tension values in patients in groups 1 and 2. For a high parasternal approach, the transducer was positioned in the second or third left intercostal space, rotated counterclockwise, and directed inferiorly or slightly superiorly. In this plane the ducus arteriosus was imaged above the junction of the left pulmonary artery with the main pulmonary trunk as reported previously.³

If this standard parasternal approach failed to visualise the ducus along its entire length we used another plane. The transducer was placed just below the right or left clavicle. Then it was rotated to visualise the long axis of the aortic arch—clockwise when the arch was left sided and counterclockwise when the arch was right sided. Next the transducer was directed inferiorly to visualise the ducus, the main pulmonary artery, and the aortic arch in the same cut.

Doppler interrogation was performed during simultaneous visualisation, with the sample volume placed in the middle of the ducus when it was widely patent and not tortuous, and at the pulmonary end, in the middle, and towards the aortic end when it was tortuous. Care was taken to place the sample volume at the same site in the ducus before and after the

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**Table Patient data**

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Diagnosis</th>
<th>Age (days) at PGE₁ infusion</th>
<th>DA shape</th>
<th>DA appearance before PGE₁</th>
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<td>T</td>
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<td>Group 4</td>
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Infusion of prostaglandin E1. Previous reports of the closure process in normal newborn infants, suggest that narrowing of the entire length of the ductus should be regarded as prominent when the ductus is <2 mm in diameter along its entire length. Similarly, we judged localised narrowing of the ductus to be prominent when the high velocity jet more than 2 m/s was directed superiorly from the localised narrowed portion of the ductus or if a characteristic non-phasic continuous flow of low velocity was recorded upstream from the narrowed portion at an intercept angle of <50° or both (fig 1). We regarded other degrees of localised intraluminal narrowing on imaging to be slight. When no lumen was visible and Doppler showed no left to right shunting, closure of the duct was diagnosed. The Doppler profile and electrocardiograms were recorded simultaneously at 100 mm/s and stored on video tape for later analysis.

Fig 1  (a and c) Long axis plane of the ductus showing localised narrowing in the middle (arrow). (b) Ductal flow profile indicating the left to right shunt flow of high velocity toward the transducer at a sampling site within the localised narrowing. (d) Non-phasic flow of low velocity upstream of the narrowing. Note the difference in flow velocity profile seen at two sampling sites within the ductus. A, anterior; P, posterior; S, superior; I, inferior; M-PA, main pulmonary artery; L-PA, left pulmonary artery; DA, ductus arteriosus; Des Ao, descending aorta.
Flow toward the transducer was displayed above the baseline, whereas flow away from the transducer was displayed below it.

**Statistical Analysis**

A two tailed Student's t test was used for statistical analysis of the difference of mean values between the two groups.

**Results**

**Ductal Morphology and Flow Profiles Before Prostaglandin E, Infusion**

The ductus could be clearly visualised along its entire length from a high parasternal approach in two planes in all patients except for two with a closed ductus, seven with a tortuous ductus in whom it was not possible to obtain an adequate imaging by the standard parasternal plane (fig 2), and two patients who had a cylindrical ductus. Ten patients had a ductus widely patent along its entire length, ranging from 3 to 7.5 mm (mean 5.3 mm) in the widest inner diameter. Of the remaining 13 patients with patent ducts, ductal narrowing was seen in the localised portion in 10 and along its entire length in three patients (table).

The Doppler method showed continuous left to right shunt flow within the ductus in all patients with ductus dependent pulmonary blood flow (group 1). A change in direction in the continuous velocity pattern was noted within tortuous ducts. In the other groups of patients with a patent ductus, ductal shunt flow profiles ranged from continuous left to right shunting to right to left shunting. In 14 of the 15 patients with a cylindrical ductus, the angle of intercept was < 30° within the ductus. In eight patients with a tortuous ductus the angle varied considerably with the sampling site in the ductus, but in seven patients it was < 50° at the aortic end, the pulmonary end, or both. This cross sectional and Doppler echocardiographic method showed that the degree of the ductal narrowing in a localised portion or along its entire length was prominent in 10 and mild in two; another patient had a localised narrowing and the ductus was almost vertically aligned with the Doppler cursor.

**Clinical and Ductal Responsiveness to Prostaglandin E**

In 16 of the 17 patients in groups 1 and 2 arterial oxygen tension was studied after prostaglandin E, infusion. A good clinical response, that is an increase in arterial oxygen tension of ≥ 10 mm Hg, was noted.
in only the seven patients in groups 1 and 2 who had prominent localised narrowing or narrowing along the whole length of the ductus before the infusion (p < 0.001) (fig 3a).

In all of these patients ductal narrowing on cross sectional and Doppler echocardiography disappeared after the infusion (fig 4). In contrast, the remaining nine patients who had a slightly narrowed or widely patent ductus did not show any significant change in arterial oxygen tension after the infusion (fig 3b). None of the 10 patients who had a widely patent ductus before and during the infusion showed a significant change in the widest ductal diameter. In two group 3 patients (cases 18 and 19) with coarctation of the aorta, the femoral artery pulse and urine flow improved during the infusion. In one patient the systolic pressure difference between radial and femoral arteries decreased from 55 to 30 mm Hg. In both patients the ductus was widely patent and the ductal flow profile changed from a right to left shunt to a bidirectional shunt after the infusion. In the other five group 3 patients, who had a widely patent or closed ductus, we saw no major changes in overall clinical findings after the infusion. In the two patients with a closed ductus, the ductus remained closed even when a high dose of prostaglandin E₁ (0.1 μg/kg/min) was given. In one patient (group 4) who had obstructive total anomalous pulmonary venous connection, the infusion resulted in an apparent improvement in pulmonary oedema on serial chest x-ray films obtained 10 hours later and an increase in urine flow. This coincided with ductal dilatation and an increase in ductal right to left shunting (fig 5).

Discussion

In patients who did not respond to prostaglandin E₁, echocardiography combined with Doppler echocardiography showed that the ductus was widely patent or only slightly narrowed before prostaglandin E₁ infusion. Furthermore, the infusion had no effect on ductal diameter in any patient with a widely patent ductus. These data confirm the hypothesis that the diameter to which prostaglandin E₁ will dilate the ductus is limited. In such patients, the infusion will not produce a further increase in oxygenation or clinical improvement, though it can be administered prophylactically to prevent ductal narrowing. Nor was prostaglandin E₁ effective in patients in whom the ductus was fully closed. But the infusion was very effective in patients in whom the ductus was patent with prominent localised or generalised narrowing. The ductus may remain responsive to prostaglandin E₁ as long as the ductus is not allowed to close fully before the infusion. The number of patients that we studied was too small to conclude that this outcome will always be achieved in such cases. Further study is needed to clarify this point.

In most of the patients with ductal narrowing, intraluminal changes were noted at a localised portion before the infusion. This localised narrowing was shown to be early evidence of ductal changes leading to spontaneous closure. Cross sectional echocardiographic imaging alone provides important information of changes within the ductal lumen. However, when the degree of localised narrowing is assessed by direct imaging the dimension of the narrowing in one plane cannot be used to assess the absolute size of the narrow portion and if the narrowed portion is < 2 mm in diameter it may fall outside the range of lateral resolution of the equipment being used. In the present study, the Doppler method could be used to confirm the ductal patency in patients with narrowing along the entire length of...
the ductus. This technique also provided additional information on the degree of the localised narrowing within the ductus. A high velocity jet was detected within and downstream from the narrowed portion. The flow velocity seen upstream of a localised narrowing was low and was usually non-phasic. Smallhorn and Freedom found that in patients with obstructive total anomalous venous connection the Doppler determined flow was non-phasic with a low velocity and turbulent with a high velocity, respectively, in the areas proximal and distal to the site of obstruction. Thus the characteristic flow profiles seen in patients with prominent localised narrowing seem to reflect the actual narrowing within the ductus. But this Doppler approach is not accurate in patients in whom the ductus is imaged in a near vertical position to the Doppler cursor.

In two patients in group 3 with coarctation of the
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Fig 5  Cross sectional echocardiograms and Doppler echocardiograms in a patient with obstructive total anomalous pulmonary venous connection. (a) Localised narrowing in the ductus (arrow) in its middle portion before infusion of prostaglandin E,

(b) Ductus was widely patent during the infusion (c and d) Right to left ductal shunt flow away from the transducer was predominant before and during the infusion. Ductal dilatation resulted in laminar right to left ductal shunt flow. R-PA, right pulmonary artery; L-PA, left pulmonary artery; Ao, aorta; see legend to fig 1 for other abbreviations.

aorta, a right to left ductal shunt became bidirectional after the infusion. This raises the possibility that the additional left to right shunt and diminished radiofemoral gradient are a consequence of diminished coarctation in such cases.

Freedom et al reported that prostaglandin E,

infusion resulted in severe pulmonary oedema with considerable respiratory distress in one patient who had visceral heterotaxia, asplenia, and complex congenital heart disease including pulmonary atresia and an obstructive total anomalous pulmonary venous connection. In the patient with obstructive total anomalous pulmonary venous connection and uncomplicated pulmonary outflow tract obstruction included in this study, the pulmonary oedema and urine flow improved within 10 hours of the infusion. The major change here may be that from a turbulent jet to a more laminar jet suggesting that a larger volume is passing through the ductus from the pulmonary artery to the aorta. Therefore, the
Responsiveness of the ductus arteriosus to prostaglandin E₁
difference in the clinical response to prostaglandin E₁
between Freedom’s case¹⁶ and ours seems to relate to
the direction of shunt flow across the ductus and its
flow volume, consequent on the presence or absence of
pulmonary valve atresia.

We thank Miki Sakakibara, Harumi Kawai, and
Masahiro Ohe for technical assistance.

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